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Variant: NM_000162.5(GCK):c.1133C>T (p.Ala378Val)

Version: 1.1

CA341585

21076 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: ee600241-27a2-46f8-8e47-92684c9a911a
Approved on: 2023/8/8
Published on: 2023/8/8

HGVS expressions

NM_000162.5(GCK):c.1133C>T (p.Ala378Val)
NM_000162.5:c.1133C>T
NC_000007.14:g.44145617G>A
CM000669.2:g.44145617G>A
NC_000007.13:g.44185216G>A
CM000669.1:g.44185216G>A
NC_000007.12:g.44151741G>A
NG_008847.1:g.48807C>T
NG_008847.2:g.57554C>T
ENST00000395796.8:c.*1131C>T
ENST00000616242.5:c.*253C>T
ENST00000683378.1:n.359C>T
ENST00000336642.9:c.167C>T
ENST00000345378.7:c.1136C>T
ENST00000403799.8:c.1133C>T
ENST00000671824.1:c.1196C>T
ENST00000672743.1:n.145C>T
ENST00000673284.1:c.1133C>T
ENST00000336642.8:c.185C>T
ENST00000345378.6:c.1136C>T
ENST00000395796.7:c.1130C>T
ENST00000403799.7:c.1133C>T
ENST00000437084.1:c.1082C>T
ENST00000459642.1:n.513C>T
ENST00000616242.4:c.1130C>T
NM_000162.3:c.1133C>T
NM_033507.1:c.1136C>T
NM_033508.1:c.1130C>T
NM_000162.4:c.1133C>T
NM_001354800.1:c.1133C>T
NM_001354801.1:c.122C>T
NM_001354802.1:c.-8C>T
NM_001354803.1:c.167C>T
NM_033507.2:c.1136C>T
NM_033508.2:c.1130C>T
NM_033507.3:c.1136C>T
NM_033508.3:c.1130C>T

NM_001354803.2:c.167C>T

Pathogenic

Met criteria codes 8

PM3_Supporting PP1_Strong PM2_Supporting PS4 PM5 PP2 PP3 PP4

Not Met criteria codes 1

PM1

Evidence Links 0

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The variant in the glucokinase gene, GCK, causes an amino acid change of alanine to valine at codon 378 (p.(Ala378Val)) of NM_000162.5. GCK is defined by the ClinGen MDEP as a gene that has a low rate of benign missense variation and has pathogenic missense variants as a common mechanism of disease (PP2). This variant is also predicted to be deleterious by computational evidence, with a REVEL score of 0.967, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent in gnomAD v2.1.1 (PM2_Supporting), and was identified in 9 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMIDs: 14578306, 25935773, internal lab contributors). One of these individuals has a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (internal lab contributors). It has also been detected in an individual with neonatal diabetes who was homozygous for this variant and had antibody-negative diabetes (PM3_Supporting, PMID: 14578306). This variant also segregated with diabetes, with at least 4 informative meioses in 4 families with MODY (PP1_Strong; internal lab contributors). Additionally, another missense variant, c.1132G>A (p.Ala378Thr) has been interpreted as pathogenic by the ClinGen MDEP and p.Ala378Val has a greater Grantham distance (PM5). In summary, c.1133C>T meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.2.0, approved 6/7/2023): PP1_Strong, PP4, PS4, PM5, PP2, PP3, PM2_Supporting, PM3_Supporting.

Met criteria codes

PM3_Supporting	✔	This variant has been detected in an individual with neonatal diabetes who was homozygous for this variant and had negative antibodies (PM3_Supporting, PMID: 14578306)
PP1_Strong	✔	This variant segregated with diabetes, with at least 4 informative meioses in 4 families with MODY (PP1_Strong; internal lab contributors).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PS4	✔	This variant was identified in 9 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes (PS4; PMIDs: 14578306, 25935773, internal lab contributors).
PM5	✔	Another missense variant, c.1132G>A (p.Ala378Thr) has been interpreted as pathogenic by the ClinGen MDEP and p.Ala378Val has a greater Grantham distance. (PM5).

PP2		✔	GCK is defined by the ClinGen MDEP as a gene that has a low rate of benign missense variation and has pathogenic missense variants as a common mechanism of disease (PP2)
PP3		✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.967, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP4		✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6%) (internal lab contributors).

Not Met criteria codes

PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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